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# Response of Focus of Origin of Experimental Ventricular Extrasystoles to Warming or Cooling.

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Extrasystoles show the phenomenon of coupling, that is, in a given individual there is a constant interval between the extrasystole and the preceding beat. This is accepted as proof of a close relationship between them, the preceding beat releasing the extrasystole in some way.

According to one group of observers the releasing beat, after having spread over the heart, reënters a small path in a circumscribed area which has been traversed before, causing a second response. Others believe that in a small "island" within the heart conduction is possible in one direction only (unidirectional block). The stimulus enters the island only on one side and on leaving this area after some delay it excites neighboring fibers causing an extrasystole. According to a third hypothesis the releasing beat initiates an abnormal, heterogenetic stimulus formation in some center.

A reëntry mechanism, caused by unidirectional block has been demonstrated in experiments on muscle strips[1] and, under rare conditions, in the mammalian heart *in situ*.[2] However there is little to support the assumption that this mechanism prevails in the formation of the majority of the extrasystoles daily encountered in patients.

Piccione and Scherf[3] demonstrated that the application of hypertonic solutions of sodium chloride or barium chloride on the epicardium or subepicardially is followed by paroxysmal tachycardias and extrasystolic arrhythmias similar to the various clinical types. The extrasystoles show fixed coupling. A specific ion effect is involved.

The effect of cooling or warming the area of the exposed heart upon which the salt solution was applied is reported in this paper. The influence on the resulting arrhythmia received particular attention. Warming or cooling was accomplished by sending water with a temperature of 150°-175°F or 50 -60 F respectively through a copper thermode. The apex of the thermode had a diameter of 4 mm. The experiments were performed on 26 dogs under nembutal anesthesia (0.5 cc per kg) with artificial respiration.

On heating the focus of origin the number of extrasystoles, already present, was regularly increased so that tachycardias appeared instead of coupled beats; if a tachycardia was present, its rate increased. When extrasystoles with fixed coupling or tachycardias failed to appear after the application of salt solution, they developed if heat were applied to this area. On cooling the focus, the rate of a tachycardia, when present, slowed and extrasystoles were abolished; however, they reappeared following an interval of about 40 sec after the cooling was stopped.

The first tracing in Fig. 1 (4,13,1942) shows a paroxysmal ventricular tachycardia, which appeared after the subepicardial injection of 0.1 cc of a 10% solution of sodium chloride to the region of the conus of the right ventricle. The rate of the tachycardia was 187. Warming the injected area with the thermode increased the rate to 214. The white irregular perpendicular lines indicate the beginning of warming. On interrupting this the original rate returned, but rewarming the area again increased the rate.

The second tracing in Fig. 1 (1,13,1941) shows a trigeminal rhythm which appeared after injecting 0.1 cc of a 30% solution of sodium chloride into a circumscribed area of the conus of the right ventricle. The dis-

1 Schmitt, F. O., and Erlanger, J., *Am. J. Physiol.*, 1921, **87**, 326.

2 Scherf, David, *Arch. Int. Med.*, 1941, **67**, 372.

3 Piccione, F. V., and Scherf, David, *Bull. N. Y. Med. College, Flower and Fifth Ave. Hosps.*, 1940, **3**, 83.

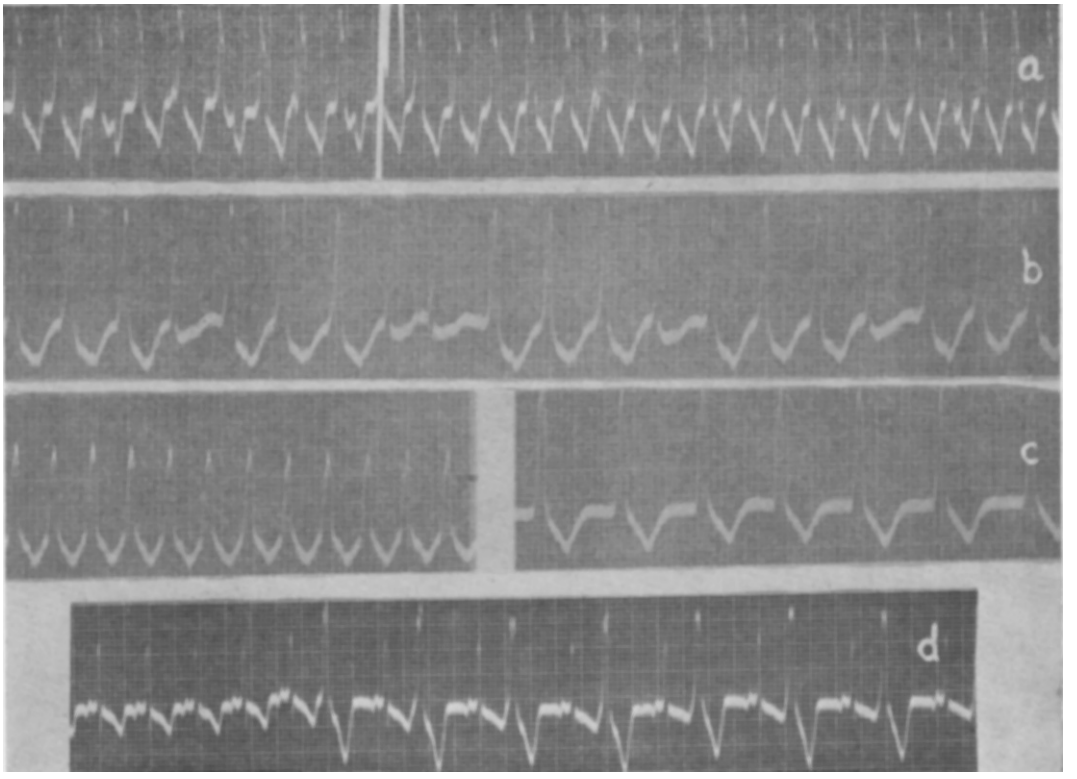


FIG. 1.

Fig. 1a shows a ventricular tachycardia following subepicardial injection of sodium chloride; the rate increases during application of heat to the injected area.

Fig. 1b shows a trigeminal rhythm following subepicardial injection of sodium chloride; the first part of Fig. 1c shows the increase in rate during warming, the second part the decrease in rate during cooling the injected area.

Fig. 1d shows a bigeminal rhythm which appeared exclusively and repeatedly during warming an area of the conus of the right ventricle on which sodium chloride was injected subepicardially.

tance between two extrasystoles was constant, 0.36 second (rate: 166 per min). After warming the area of injection a paroxysmal tachycardia appeared (first part of the third tracing in Fig. 1) and the distance between two extrasystoles fell to 0.26 second (rate: 230), during cooling (second part of the third tracing) the rate fell to 115. A few seconds later the extrasystoles disappeared completely.

The fourth tracing in Fig. 1 was obtained in an experiment on 5,14,1942. This time the subepicardial injection of 0.1 cc of a 10% solution of sodium chloride into the conus area of the right ventricle failed to produce extrasystoles. After warming the area where the injection had been given, short runs of extrasystoles in groups and bigeminal rhythm appeared. The fourth tracing in Fig. 1 shows a regular bigeminy. Each extrasystole follows the normal beat after an interval of 0.24 second. The extrasystoles appeared repeatedly 2 or 3 seconds after warming was begun and disappeared 4 to 6 seconds after the removal of the thermode.

Warming areas on the surface of the heart to which no sodium or barium chloride had been applied, did not evoke extrasystoles.

It is difficult to conceive that warming the area of injection accelerates an existing circus or reëntry mechanism, or even initiates them, if they were not previously present. These results seem to be explained better by the assumption that the extrasystoles are due to a disturbance of stimulus formation. If the

latter is due to formation and discharge of potential differences across a semipermeable membrane, this process may be changed depending on the presence of certain electrolytes and it may be accelerated or even initiated on warming and slowed down or abolished by cooling the center of extrasystoles formation.

*Conclusions.* Coupled extrasystoles appear in dogs following epicardial or subepicardial application of hypertonic solutions of sodium or barium chloride on circumscribed areas. Warming of the injected area increases the number and the rate of the extrasystoles or causes them to appear even if they were not present after the injection. Cooling the area of injection slows the rate of formation of extrasystoles or abolishes them completely.

These results can be explained satisfactorily by assuming a heterogenetic stimulus formation in the treated area.

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## Inhibiting Effect of Methionine, Choline and Betaine on Rabbit's Susceptibility to Infection with Vaccinia.*

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In the course of experiments to determine what factors in a rabbit's diet are essential to virus multiplication it was observed that the subcutaneous injection of methionine increased the rabbit's resistance to dermal infection with vaccinia. Six experiments have been performed with methionine. The results of a typical experiment are shown in Table I. In this experiment and others described below rabbits weighing approximately 2 kg were used. The experimental rabbits received 300 mg of methionine subcutaneously daily for 2 days preceding and 5 days following vaccination. In other experiments the conditions of the experiment were varied as to the amount of methionine and the times at which it was given. These experiments showed that if the methionine was given 48 hr before vaccination, the resistance was increased 14 fold; if given immediately following vaccination, the increase was 10 fold; if delayed until 48 hr after vaccination the increase was 5 fold. In addition to these quantitative changes in resistance, the lesions of the animals whose resistance had been stimulated most by methionine were smaller and disappeared approximately 24 hr earlier than did the ones of the control animals. Measurements of resistance were made by use of serial dilutions of vaccinia virus as described previously.[1] The experimental error in this method is considerably less than a 2-fold difference, hence the observed changes were highly significant.

Additional studies were then undertaken to determine what biological functional group of the methionine molecule was responsible for this effect. That it was probably not dependent on the generalized properties of the amino acids as such was indicated by the fact that glycine had no significant effect on susceptibility. Neither does the mere presence of sulfur in the molecule explain the action, for cystine did not duplicate the effect of methionine.

The chemical characteristic which seems most likely to be involved is the biologically labile methyl group. Choline and betaine share with methionine the property under proper circumstances of possessing an easily transferable methyl group,[2] and these substances were therefore investigated in a series of 5 experiments. When given 48 hr before

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1 Sprunt, D. H., *J. Exp. Med.*, 1942, **75**, 297.

2 du Vigneaud, V., *Biological Symposia*, 1941, **5**, 234.